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A Small Deletion of 16q23.1→16q24.2 [del(16)(q23.1q24.2).ish del(16)(q23.1q24.2)(D16S395+, D16S348–, P5432+)] in a Boy With Iris Coloboma and Minor Anomalies

Walter Werner,[1]* Sabine Kraft,[1] David F. Callen,[2] Oliver Bartsch,[1] and Georg Klaus Hinkel[1]
[1]Institut für Klinische Genetik, Universitätsklinikum C.G.Carus, TU Dresden, Germany
[2]Department of Cytogenetics and Molecular Genetics, Adelaide Children's Hospital, Adelaide, Australia

We report on a 5-year-old boy with bilateral coloboma of iris, short stature, moderate developmental delay, and a few minor craniofacial anomalies. High-resolution GTG banding showed a small distal deletion of one chromosome 16 [del(16)(q23.1q24.2)]. Molecular refinement of the deletion breakpoints yielded that the proximal breakpoint at 16q23.1 is located between loci D16S395 (present) and D16S348 (absent). Comparison with previously published cases of deletion 16q demonstrated that the clinical phenotype is not a recognizable 16q- syndrome and different from the two cases of deletions of 16(q22.1 to q24.1) described by Callen et al. [1993]. Evidently, deletion 16(q23.1q24.2) has a milder phenotypic effect than other interstitial and distal 16q deletions. Am. J. Med. Genet. 70:371–376, 1997.

KEY WORDS: 16q deletion; del(16)(q23.1-q24.2); coloboma of iris; mild developmental delay; minor anomalies

INTRODUCTION

Interstitial and distal deletions of the long arm of chromosome 16 are rare. To our knowledge, 19 cytogenetically well-documented cases of a 16q deletion have been published [Fryns et al., 1977, 1981; Lin et al., 1983; Elder et al., 1984; Hoo et al., 1985; Rivera et al., 1985; Krauss et al., 1987; Cooke et al., 1987; McDonald et al., 1987; Natt et al., 1987; Witt et al., 1988; Naritomi et al., 1988; Natt et al., 1989; Casamassima et al., 1990; Edelhoff et al., 1991; Fujiwara et al., 1992; Schuffenhauer et al., 1992; Callen et al., 1993]. Most case reports of a 16q deletion deal with deletions of region 16q12→q22, which, in general, have a phenotype similar to the well-established 16q- syndrome [Fryns et al., 1981; Lin et al., 1983; Naritomi et al., 1988]. In contrast to deletions 16(q12 q22), there are only two reports of deletions of the distal region 16q23→q24.1 [McDonald et al., 1987; Callen et al., 1993]. Deletions of the terminal region 16q24.2q24.3 have not been reported so far. Possibly, small terminal 16q deletions can escape detection.

We describe a deletion 16(q23.1q24.2) observed in a 5-year-old boy with iris coloboma, short stature and moderate developmental retardation.

This 16q deletion is the most distal one reported to date. It adds new data to the delineation of clinical phenotypes associated with specific regions of 16q.

Clinical Report

The patient is the second child of healthy, nonconsanguineous parents. He was born to a 37-year-old mother and a 39-year-old father. The mother took birth control pills until week 12 of gestation unaware of the pregnancy. Birth was at week 41 by caesarean section for growth failure, with a birth weight of 2,800 g (–1.15 SDS), length of 48 cm (–1.18 SDS), and OFC of 35 cm. Postnatal adaptation was uneventful. The broad, prominent forehead was noted soon after birth. Developmental delay was noted at the age of 2 years.

On clinical examination at age 5 4/12 years in our institution, height was 106.2 cm (–1.79 SDS), weight was 15.3 kg (–2.49 SDS), and OFC was 53.0 cm (+0.63 SDS). He had bilateral coloboma of iris, a broad prominent forehead without a palpable metopic ridge, bushy eyebrows, and a large nose and mouth. His hair was brown and of normal texture with a high anterior hairline. His body was well proportioned (Fig. 1a–d), and hands and feet were well formed. There were undescended testes and a relative large penis. Brain MRT, hearing tests, and biochemical examinations including haptoglobin were normal.

Prometaphase chromosome analysis by GTG band-

*Correspondence to: Walter Werner, Institut für Klinische Genetik, Universitätsklinikum C.G.Carus, TU Dresden, Fetscherstrasse 74, D-01307 Dresden, Germany.

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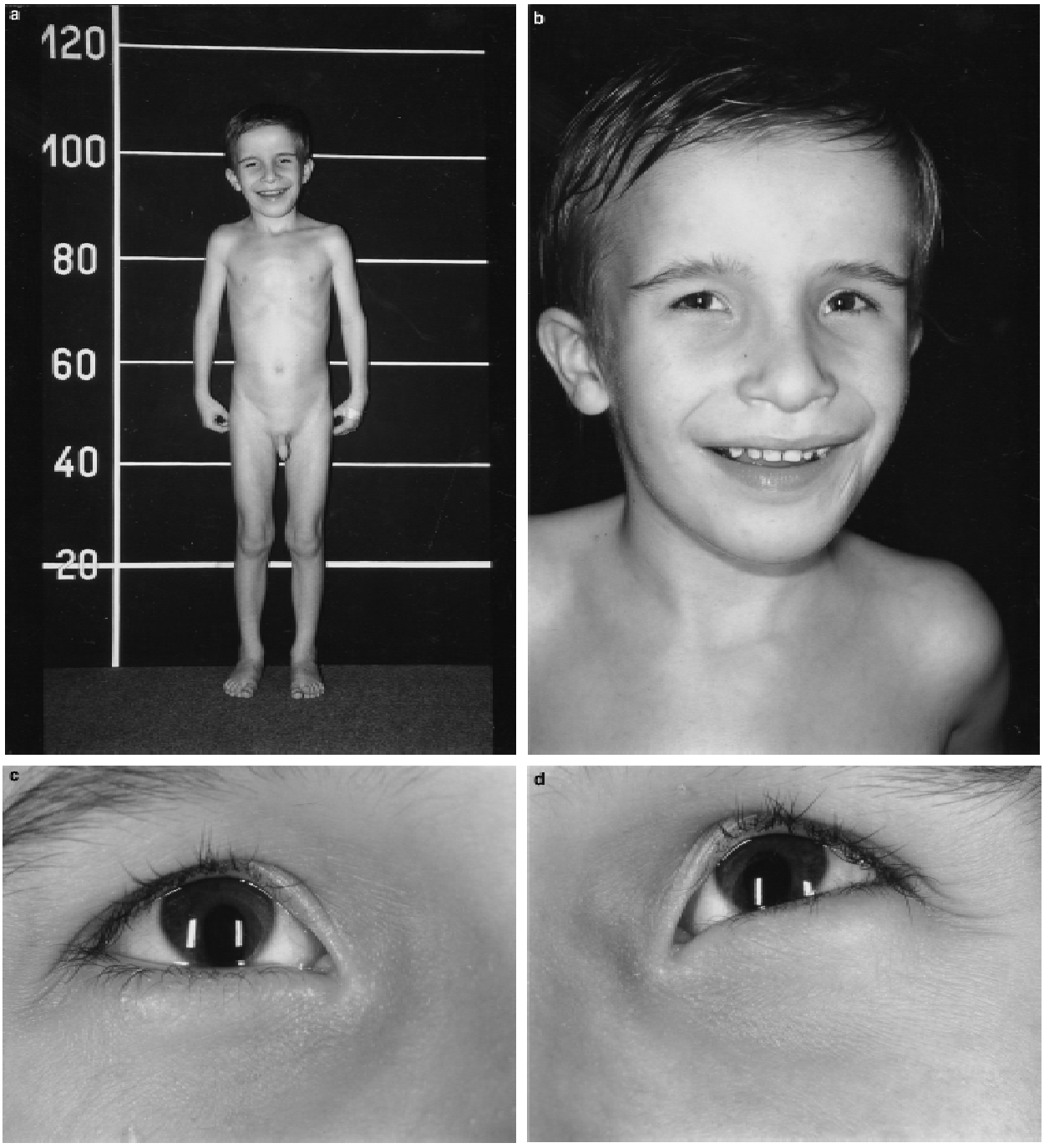

Fig. 1. **a**: General appearance of the patient at age 5 4/12 years; note short stature and relative macrocephaly. **b**: Detail of the face showing broad forehead, bilateral coloboma of iris, and large nose and mouth. **c,d**: Detail of the right and left eye, respectively, showing bilateral coloboma of iris.

ing showed a 46,XY, del(16)(q23.1q24.2) karyotype (Fig. 2). The presence of a distal interstitial 16q deletion, and not an unbalanced 16q translocation or a cryptic balanced 16q translocation, was confirmed by fluorescence in situ hybridization (FISH).

FISH with the specific 16q subtelomeric probe P 5432 (Oncor Inc., Gaithersburg, MD, subcloned from a 250 kb YAC clone, localisation: 16q24→qter), demonstrated two identical fluorescent signals at the terminal ends of both the normal and the deleted chromosome 16 (Fig. 3). FISH localisation experiments with 16q specific cosmids documented that the cosmid c33G11 (locus D16S395) was present on the deleted 16q chromosome, while the cosmid c301B4 (locus D16S348) was absent. This placed the proximal molecular breakpoint of the deletion between D16S395 and D16S348 within 16q23.1→q23.3 [Callen et al., 1992]. The distal deletion breakpoint is still to be resolved by further FISH localisation experiments.

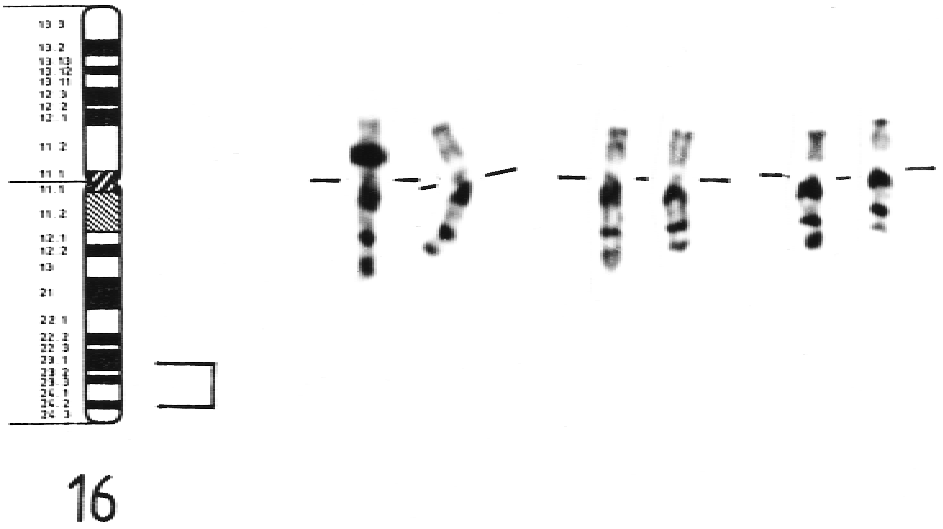

Fig. 2. GTG-banded partial karyotypes of the patient showing the deletion 16(q23.1q24.2). Normal homologues (left) and deleted 16 (right). Breakpoints of the 16q deletion are marked on the schematic representation of chromosome 16.

Parental chromosomes were normal, thus, the 16q deletion of the propositus is de novo.

DISCUSSION

Including this report we are aware of 20 case reports of partial monosomy 16q (Table I). Summarizing the cytogenetic findings on all 16q deletions, it can be concluded that a viable partial monosomy has been observed for each region of 16q (q11.1 to q24.2) (Fig. 4) with very little or no information available on the very distal segment 16q24.2q24.3.

Recently, Callen et al. [1990] reexamined the terminal deletion 16(q22) reported by Taysi et al. [1978], and showed that the del(16)(q22) indeed represents an apparently balanced translocation t(4;16)(q35;q22.1). Similarly, the terminal deletion 16(q21) of Fryns et al. [1977] could possibly represent either a cryptic balanced 16q translocation or an interstitial 16q deletion retaining the terminal region 16q24.2q24.3. Furthermore, Casamassima et al. [1990] mentioned in their case report that the interstitial deletion 16(q13q22) was originally reported as a terminal deletion del(16(q22)) by Brenholz et al. [1982]. In view of these findings, Callen et al. [1993] suggested that partial monosomies of the terminal region 16q24.2q24.3 could possibly be embryonic lethals. Rack et al. [1993] identified a familial 16q+ chromosome in the female patient PL and in her DZ twin sons as an unbalanced translocation [der(16)t(2;16)(q37.1;q24.3)]. The 16q breakpoint was localised within 230 kb of the 16q telomere. Presently, we realize the need of additional cases of very distal 16q rearrangements to confirm the suggestion of Callen et al. [1993]. In this context, the molecu-

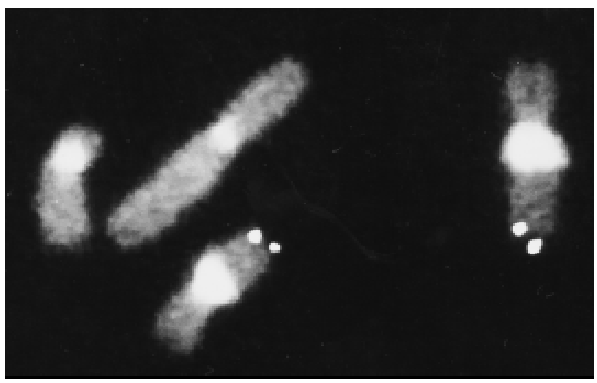

Fig. 3. FISH with the 16q terminal probe P5432 (Oncor Inc.) shows identical fluorescent signals on the normal and on the deleted chromosome 16 (arrows). Fluorescent detection using FITC-conjugated antibodies and DAPI-counterstaining.

TABLE I. Breakpoint Location of Published 16q Deletions

Case	references		Karyotype
1	Hoo et al. [1985]	a/b	46,XX,del(16)(q11.1q12.1)
2	Krauss et al. [1987]		46,XX,del(16)(q11.1q13)
3	Elder et al. [1984]	a/b	46,XX,del(16)(q12.1q13)
4	Schuffenhauer et al. [1992]	ID 1	46,XY,del(16)(q12.1q13).ish
5	Callen et al. [1993]	ID 2	46,XY,del(16)(q12.2q21).ish
6	Fryns et al. [1981]		46,XX,del(16)(q13q22)
7	Lin et al. [1983]		46,XY,del(16)(q13q22)
8	Naritomi et al. [1988]		46,XX,del(16)(q13q22)
9	Casamassima et al. [1990]		46,XY,del(16)(q13q22)
10	Edelhoff et al. [1991]		46,XY,del(16)(q13q22)
11	Witt et al. [1988]	ID 3	46,XX,del(16)(q13q22).ish
12	Fryns et al. [1977]		46,XX,del(16)(q21)
13	Rivera et al. [1985]		46,XX,del(16)(q21q23)
14	Callen et al. [1993]	ID 4	46,XX,del(16)(q21q22.2).ish
15	Cooke et al. [1987]	ID 5	46,XX,del(16)(q22.1q22.3).ish
16	Fujiwara et al. [1992]		46,XX,del(16)(q22.1q22.3)
17	Natt et al. [1987, 1989]		46,XY,del(16)(q22.1q22.3).ish
18	McDonald et al. [1987]	ID 6	46,XX,del(16)(q22.1q23.3).ish
19	Callen et al. [1993]	ID 7	46,XX,del(16)(q23.1q24.1).ish
20	Present case		46,XY,del(16)(q23.1q24.2).ish

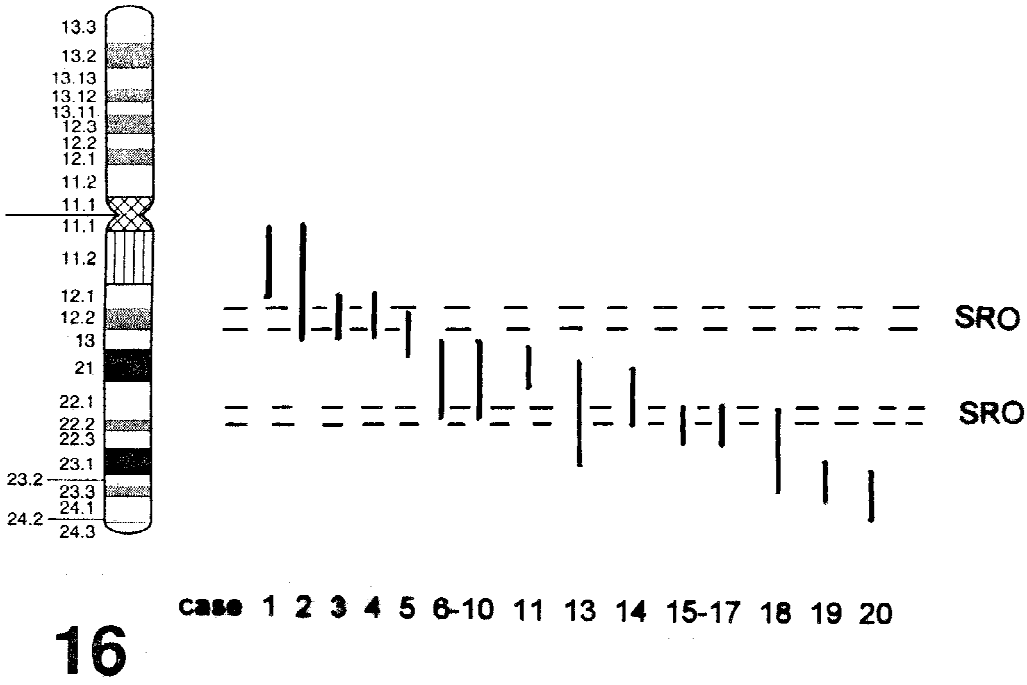

Fig. 4. Schematic representation of the breakpoint location and the extent of all 16q deletions so far reported. The dark lines indicate the deleted 16q segments. The regions between the dotted lines in the proximal region 16q12.1q12.2 and in the interstitial region 16q22.1 q22.2, respectively, could possibly correspond to the smallest region of overlap (SRO) in the 16q- syndrome. The ideogram, at the 850-band level, is from the ISCN [1995].

lar location of the distal breakpoint of our distal 16q deletion is of interest.

The breakpoint locations and the extent of all previously reported 16q deletions are illustrated in Figure 4. Concerning the 16q- phenotype, there are no striking phenotypic differences between patients with small proximal and interstitial deletions [Elder et al., 1984; Cooke et al., 1987; Natt el., 1987; Schuffenhauer et al., 1992; Fujiwara et al., 1992; Callen et al., 1993 ID 2] and patients with longer proximal and interstitial deletions [Rivera et al., 1985; Krauss et al., 1987]. Obviously, there is no clear correlation between the extent of the 16q deletions and the severity of the clinical picture of these patients. This seems also to be true for the present case. Moreover, the clinical manifestations appear to be related to critical regions involved.

We present the cytogenetic and molecular cytogenetic findings on a distal 16q deletion [del(16)(q23.1q24.2)] in a 5-year-old boy with iris coloboma, short stature, and mild developmental delay. The proximal deletion breakpoint was mapped between D16S395 and D16S348, whereas the distal deletion breakpoint still has to be resolved. The present deletion shows overlap with two other distal 16q deletions, i.e., with del(16)(q22.1q23.3) [McDonald et al., 1987; ID 6 of Callen et al., 1993] and del(16)(q23.1q24.1) [D 7 of Callen et al., 1993], respectively. The distal breakpoint of our deletion appears to be more distal.

The correlation of the phenotype with that of previously reported 16q deletions (Table II) shows clear-cut differences to the 16q- syndrome [del(16) (q12q22)]. The most common anomalies of the 16q- syndrome are failure to thrive, severe psychomotoric retardation, hypotonia, postnatal growth retardation, and a characteristic facial appearance. The latter is formed by high forehead with prominent metopic suture, large fontanelle, microcephaly, hypertelorism, apparently low-set abnormally modeled ears, micrognathia, and a short neck.

To date, it seems hardly possible to get one smallest region of overlap (SRO) as crucial region for the 16q-syndrome (Table II, Fig. 4). To explain the contradictory findings in the 16q- syndrome, one could assume that there are two noncontiguous regions (SRO) crucial for the 16q- syndrome, one in 16q12.1q12.2 and the other one in 16q22.1q22.2 (Fig. 4).

The correlation of the phenotype with that of the two other cases of distal 16q deletions (cases 18 and 19) (Table II) shows a few common manifestations, including mild developmental delay, postnatal growth retardation, and broad forehead. Iris coloboma has not been reported in any case of a 16q deletion.

Obviously, the present deletion of 16q23.1q24.2 has a less profound phenotypic effect than the other two overlapping deletions of the distal portion of the chromosome 16 long arm. The cause(s) of these phenotypic differences remain unclear at present, i.e., whether they reflect differences in molecular breakpoints, or merely reduced penetrance. The bilateral coloboma of iris in this patient could possibly result from deletion of gene(s) within 16q23.1q24.2. However, coloboma of iris has been reported in 36 other chromosome abnormalities and is a non-specific sign. The distal interstitial deletion of 16q23.1q24.2 present here may be helpful for the delineation of clinical phenotypes associated with deletions of the distal portion of the chromosome 16 long arm.

TABLE II. Summary of Manifestations of Patients With Various 16q Deletions

	Deletion of 16q region				
		q12q22			
	q21q?	cases	q22.1q23.3	q23.1q24.1	q23.1q24.2
Finding	case 12	2–10 + 13–16[a]	case 18	case 19	case 20
Growth/development					
Small for date	–	4/14	–	–	–
p.n. growth retardation	+	12/14	+	–	+
Failure to thrive	+	14/14	+	+	–
Microcephaly	–	10/14	+	–	–
Craniofacial					
High forehead	+	14/14	+	+	+/–
Prominent metopic suture	+	11/13	–	–	–
Large anterior fontanelle	+	11/11	–	+	–
Hypertelorism	+	11/13	–	+	–
Broad nasal bridge	+	12/14	–	–	–
Low-set, dysm. ears	+	12/14	–	+	–
High arched, cleft, palate	–	11/12	–	+	–
Micrognathia	+	8/12	–	+	–
Coloboma of iris	–	0	–	–	+
Skeletal					
Short neck	+	11/12	–	–	–
Narrow thorax	+	10/12	–	–	–
Broad first toe	+	11/11	+	+	–
Flexed fingers	+	4/8	–	+	–
Small hands and feet	–	6/13	–	+	–
Neurological					
Mental retardation	?	14/14	+	+	+/–
Hypotonia	+	13/13	+	–	+
Visceral					
Cong. heart defect	+	8/13	–	–	–
Gastrointestinal anomalies	?	6/13	–	–	–
Renal anomalies	–	3/11	–	–	–
Sex	F	9F:5M	F	F	M

[a]Cases of Hoo et al. [1985] and of Natt et al. [1987, 1989] were not included because of different phenotypes to the 16q- syndrome.

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REFERENCES

Brenholz P, Wilmot P, Shapiro LR (1982): Fragile site on chromosome 16 and the 16q- syndrome. Am J Hum Genet 34:119A.

Callen DF, Baker EG, Lane SA (1990): Re-evaluation of GM 2346 from a del(16)(q22) to t(4;16)(q35;q22.1). Clin Genet 38:466–468.

Callen DF, Doggett NA, Stallings RL, Whitmore SA, Lane SA, Nancarrow J, Chen LZ, Apostolou S, Thompson AD, Baker E, Yang S, Sutherland GR (1992): A high-resolution cytogenetic-based physical map of human chromosome 16. Genomics 13:1178–1185.

Callen DF, Eyre H, Lane S, Shen Y, Hansmann I, Spinner N, Zackai E, McDonald-McGinn D, Schuffenhauer S, Wauters J, Van Thienen M-N, Van Roy B, Sutherland GR, Haan EA (1993): High resolution mapping of interstitial long arm deletions of chromosome 16: Relationship to phenotype. J Med Genet 30:828–832.

Casamassima AC, Klein RM, Wilmot PL, Brenholz P, Shapiro LR (1990): Deletion of 16q with prolonged survival and unusual radiographic manifestations. Am J Med Genet 37:504–509.

Cooke A, Tolmie J, Darlington W, Boyd E, Tomson R, Ferguson-Smith MA (1987): Confirmation of a suspected 16q deletion in a dysmorphic child by flow karyotype analysis. J Med Genet 24:88–92.

Edelhoff S, Maier B, Trautmann U, Pfeiffer RA (1991): Interstitial deletion of 16(q13q22) in a newborn resulting from a paternal insertional translocation. Ann Genet (Paris) 34:85–89.

Elder FFB, Ferguson JW, Lockhart LH (1984): Identical twins with deletion 16q syndrome: Evidence that 16q12.2-q13 is the critical band region. Hum Genet 67:233–236.

Fryns JP, Melchior S, Jaeken J, Van den Berghe H (1977): Partial monosomy of the long arm of chromosome 16 in a malformed newborn: Karyotype 46, XX,del(16)(q21). Hum Genet 38:343–346.

Fryns JP, Proesmans W, Van Hoey G, Van den Berghe H (1981): Interstitial 16q deletion with typical dysmorphic syndrome. Ann Genet (Paris) 24:124–125.

Fujiwara M, Yoshimoto T, Morita Y, Kamada M (1992): Interstitial deletion of chromosome 16q: 16q22 is critical for 16q-syndrome. Am J Med Genet 43:561–564.

Hoo JJ, Lowry RB, Lin CC, Haslam RHA (1985): Recurrent de novo interstitial deletion of 16q in two mentally retarded sisters. Clin Genet 27:420–425.

ISCN (1995): An International System for Human Cytogenetic Nomenclature: Recommendations of the International Standing Committee on Human Cytogenetic Nomenclature. Cytogenet Cell Genet Suppl:1–114.

Krauss CM, Caldwell D, Atkins L (1987): Interstitial deletion and ring chromosome derived from 16q. J Med Genet 24:308–312.

Lin CC, Lowry RB, Snyder FF (1983): Interstitial deletion for a region of the long arm of chromosome 16. Hum Genet 65:134–138.

McDonald DM, Spinner NB, King MC, Emanuell BS, Zackai EH (1987): Interstitial deletion 16q in two patients: Confirmation of cytogenetics by analysis of haptoglobin levels. Am J Hum Genet 41:A132.

Naritomi K, Shiroma N, Izumikawa Y, Sameshima K, Ohdo S, Hirayama K (1988): 16q21 is critical for 16q deletion syndrome. Clin Genet 33: 372–375.

Natt E, Westphal E-M, Toth-Fejel SE, Magenis RE, Buist NRM, Rettenmeier R, Scherer G (1987): Inherited and de novo deletion of the tyrosine amino- transferase gene locus at 16q22.1q22.3 in a patient with tyrosinemia type II. Hum Genet 77:352–358.

Natt E, Magenis RE, Zimmer J, Mansouri A, Scherer G (1989): Regional assignment of the human loci for uvomorulin (UVO) and chymotrypsin B (CTRB) with the help of overlapping deletions on the long arm of chromosome 16. Cytogenet Cell Genet 50:145–148.

Rack KA, Harris PC, MacCarthy AB, Boone R, Raynham H, McKinley M, Fitchett M, Towe CM, Rudd P, Armour JAL, Lindenbaum RH, Buckle VJ (1993): Characterization of three de novo derivative chromosomes by "reverse chromosome painting" and molecular analysis. Am J Hum Genet 52:987–997.

Rivera H, Vargas-Moyeda E, Möller M, Torres-Lamas A, Cantu JM (1985): Monosomy 16q: A distinct syndrome. Clin Genet 28:84–86.

Schuffenhauer S, Callen DF, Seidel H, Shen Y, Lederer G, Murken J (1992): De novo interstitial deletion 16(q12.1q13) of paternal origin in a 10-year-old boy. Clin Genet 42:246–250.

Taysi K, Fishman M, Sekhon GS (1978): A terminal long arm deletion of chromosome 16 in a dysmorphic infant: 46,XY,del(16)(q22). New York: Alan R. Liss, Inc., for the National Foundation–March of Dimes. BD:OAS XIV:343–347.

Witt DR, Lew SP, Mann (1988): Heritable deletion of band 16q21 with normal phenotype: Relationship to late replicating DNA. Am J Hum Genet 43:A127.